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A Test of the Transdiagnostic Dopamine Hypothesis of Psychosis Using Positron Emission Tomographic Imaging in Bipolar Affective Disorder and Schizophrenia

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← Editorial

+ Supplemental content

IMPORTANCE The dopamine hypothesis suggests that dopamine abnormalities underlie psychosis, irrespective of diagnosis, implicating dopamine dysregulation in bipolar affective disorder and schizophrenia, in line with the research domain criteria approach. However, this hypothesis has not been directly examined in individuals diagnosed with bipolar disorder with psychosis.

OBJECTIVES To test whether dopamine synthesis capacity is elevated in bipolar disorder with psychosis and how this compares with schizophrenia and matched controls and to examine whether dopamine synthesis capacity is associated with psychotic symptom severity, irrespective of diagnostic class.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional case-control positron emission tomographic study was performed in the setting of first-episode psychosis services in an inner-city area (London, England). Sixty individuals participated in the study (22 with bipolar psychosis [18 antipsychotic naive or free], 16 with schizophrenia [14 antipsychotic naive or free], and 22 matched controls) and underwent fluorodihydroxyphenyl-L-alanine ($[^{18}\text{F}]\text{-DOPA}$) positron emission tomography to examine dopamine synthesis capacity. Standardized clinical measures, including the Positive and Negative Syndrome Scale, Young Mania Rating Scale, and Global Assessment of Functioning, were administered. The study dates were March 2013 to November 2016.

MAIN OUTCOMES AND MEASURES Dopamine synthesis capacity (Ki^{cer}) and clinical measures (Positive and Negative Syndrome Scale, Young Mania Rating Scale, and Global Assessment of Functioning).

RESULTS The mean (SD) ages of participants were 23.6 (3.6) years in 22 individuals with bipolar psychosis (13 male), 26.3 (4.4) years in 16 individuals with schizophrenia (14 male), and 24.5 (4.5) years in controls (14 male). There was a significant group difference in striatal dopamine synthesis capacity (Ki^{cer}) ($F_{2,57} = 6.80$, $P = .002$). Ki^{cer} was significantly elevated in both the bipolar group (mean [SD], $13.18 [1.08] \times 10^{-3} \text{ min}^{-1}$; $P = .002$) and the schizophrenia group (mean [SD], $12.94 [0.79] \times 10^{-3} \text{ min}^{-1}$; $P = .04$) compared with controls (mean [SD], $12.16 [0.92] \times 10^{-3} \text{ min}^{-1}$). There was no significant difference in striatal Ki^{cer} between the bipolar and schizophrenia groups. Ki^{cer} was significantly positively correlated with positive psychotic symptom severity in the combined bipolar and schizophrenia sample experiencing a current psychotic episode, explaining 27% of the variance in symptom severity ($n = 32$, $r = 0.52$, $P = .003$). There was a significant positive association between Ki^{cer} and positive psychotic symptom severity in individuals with bipolar disorder experiencing a current psychotic episode ($n = 16$, $r = 0.60$, $P = .01$), which remained significant after adjusting for manic symptom severity.

CONCLUSIONS AND RELEVANCE These findings are consistent with a transdiagnostic role for dopamine dysfunction in the pathoetiology of psychosis and suggest dopamine synthesis capacity as a potential novel drug target for bipolar disorder and schizophrenia.

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Psychotic illnesses, such as schizophrenia and bipolar affective disorder, have a combined lifetime prevalence of approximately 3%.¹ The research domain criteria initiative from the National Institute of Mental Health proposes that common neurobiological mechanisms underlie symptom domains across disorders.² The neuromodulator dopamine has been implicated in the pathophysiology of psychosis in schizophrenia³⁻⁹ and psychosis in other disorders.¹⁰ Investigations using positron emission tomography (PET) have demonstrated increased striatal dopamine synthesis capacity in schizophrenia.¹¹ Dopamine synthesis capacity is also elevated in individuals at high clinical risk of psychosis,¹²⁻¹⁶ some of whom may develop bipolar affective disorder with psychosis,¹⁷ and in individuals with psychosis in the context of temporal lobe epilepsy.¹⁰ These findings suggest that elevated dopamine synthesis capacity may be transdiagnostic, underlying psychosis across disorders, rather than specific to schizophrenia. Evidence also suggests that dopamine dysfunction increases with development of psychosis¹⁵ and is greater in acute psychosis relative to remission,⁹ suggesting a state component.

Bipolar affective disorder has an approximate lifetime prevalence of 1%,¹⁸ and about half of the patients develop psychosis, predominantly in the manic phase.¹⁹ Psychotic symptoms in bipolar affective disorder respond to antipsychotic drugs (dopamine D₂/D₃ blockers), suggesting that a dopaminergic abnormality could underlie these symptoms.²⁰⁻³³ Dopamine synthesis capacity is unaltered in bipolar disorder without psychosis,³⁴ although it remains unclear if dopamine synthesis capacity is altered in individuals with bipolar disorder with a history of psychosis, whether this is related to psychotic symptoms, or how this compares with schizophrenia.

Therefore, we sought to investigate dopamine synthesis capacity indexed using fluorodihydroxyphenyl-L-alanine ([¹⁸F]-DOPA) PET imaging in individuals with bipolar psychosis. We hypothesized that (1) individuals with bipolar psychosis would have elevated striatal dopamine synthesis capacity compared with matched healthy controls and that this elevation would be comparable to that in schizophrenia and (2) striatal dopamine synthesis capacity would positively correlate with psychotic symptom severity in individuals currently experiencing psychosis, irrespective of diagnosis, in line with evidence linking dopamine dysregulation to psychotic state.^{9,15}

Methods

Ethical permission was obtained from the local ethics committee (East of England–Cambridge East National Health Service Research Ethics Committee) for this cross-sectional case-control study. All participants provided written informed consent to be included in the study. An a priori power calculation in G*power was used to determine the minimum sample size (eAppendix in the [Supplement](#)). The study dates were March 2013 to November 2016.

Participants

Patients with bipolar disorder were recruited from first-episode psychosis services in an inner-city area (London, En-

Key Points

Question Is dopamine synthesis capacity elevated in bipolar psychosis compared with controls?

Findings In this cross-sectional case-control positron emission tomographic study of 22 individuals with first-episode bipolar psychosis, 16 individuals with first-episode schizophrenia, and 22 controls, there was a statistically significant elevation in dopamine synthesis capacity in those with bipolar psychosis compared with controls. This difference was similar to that seen in schizophrenia, and there was a statistically significant association between positive psychotic symptoms and dopamine synthesis capacity in the whole sample, explaining 27% of the variance.

Meaning Dopamine synthesis capacity is elevated in bipolar psychosis and is associated with positive psychotic symptoms, irrespective of diagnosis.

gland). They were eligible for inclusion in the study if they (1) met diagnostic (*DSM-IV*) criteria for bipolar affective disorder type I as assessed by the Structured Clinical Interview for *DSM-IV* Axis I disorders,³⁵ (2) had at least one current or previous psychotic episode (defined below), and (3) demonstrated no evidence that symptoms were drug induced.

Individuals with schizophrenia were recruited from the same first-episode psychosis services, matched with the bipolar group for age (within 5 years). They were eligible for inclusion in the study if they (1) met the Structured Clinical Interview for *DSM-IV* Axis I disorders³⁵ criteria for schizophrenia, (2) had at least one current or previous psychotic episode as defined below, and (3) demonstrated no evidence that the symptoms were drug induced.

A psychotic episode was defined as at least moderate severity on one or more of the delusion (P1), hallucination (P3), and persecution (P6) items on the Positive and Negative Syndrome Scale (PANSS) lasting for at least 1 week, consistent with research definitions.¹⁷ We excluded the conceptual disorganization item, which could be confounded by mania.

Age-matched (within 5 years) healthy controls were recruited contemporaneously from the same geographical area through advertisements in local media. Healthy volunteers had no previous or current history of psychiatric illness (assessed by the Structured Clinical Interview for *DSM-IV* Axis I disorders),³⁵ no concurrent psychotropic medication use, and no family history of psychosis. Full exclusion criteria are given in the eAppendix in the [Supplement](#).

Clinical Assessments

Participants were assessed on the day of the PET scan with the PANSS,³⁶ Global Assessment of Functioning (GAF) scale,³⁷ and, in the bipolar group, Young Mania Rating Scale (YMRS).³⁸ All patients received clinical follow-up for a minimum of 18 months to determine diagnostic stability using *DSM-IV* criteria.

Medication history was recorded. Individuals were subclassified as antipsychotic naive (no current or previous treatment), antipsychotic free (not currently taking antipsychotic medication, with at least 6 weeks' washout for oral medication or 6 months' washout for depot medication), or currently treated with antipsychotics.³⁹

[¹⁸F]-DOPA PET Imaging

Imaging data were obtained on a PET scanner (Biograph 6 HiRez; Siemens) in 3-D mode. Participants were not permitted to smoke for 4 hours preceding the scan.⁴⁰ One hour before the scan, participants received 400 mg of entacapone, a peripheral catechol-*O*-methyl-transferase inhibitor, and 150 mg of carbidopa, a peripheral aromatic acid decarboxylase inhibitor, to prevent formation of radiolabeled metabolites that may cross the blood-brain barrier.⁴¹ After acquiring a computed tomographic scan for attenuation correction, approximately 160 MBq of [¹⁸F]-DOPA was administered by bolus intravenous injection 30 seconds after the start of PET imaging (eAppendix in the [Supplement](#)).

PET Image Analysis

The region-of-interest analysis was conducted masked to group status. Our primary end point was the dopamine synthesis capacity (K_i^{cer} , written previously as K_i^{42}) in the whole striatum. In view of evidence that dopaminergic alterations may be more marked in schizophrenia in the associative subdivision of striatum relative to other regions^{13,43,44} and elevated in the substantia nigra,⁴⁴ we also conducted secondary analyses of these regions. Statistical parametric mapping (SPM8; Wellcome Trust Centre for Neuroimaging⁴⁵) was used to automatically normalize a tracer-specific template,^{13,46} together with functional striatal and substantia nigra regions of interest defined in Montreal Neurologic Institute space,^{47,48} to each individual PET summation realigned image. Further details of striatal subdivisions are given in the eAppendix in the [Supplement](#). The cerebellum was used as the reference region, defined as per Martinez et al.⁴⁸ K_i^{cer} was calculated using the Patlak-Gjedde graphical approach adapted for reference tissue input function, which has been shown to have good reliability.⁴⁶ Although the reference region approach is robust to global differences in radiotracer delivery to the brain,⁴⁹ we examined the reference region (cerebellum) to see whether there was any change in standardized uptake values in the cerebellum at 95 minutes.

An exploratory voxelwise analysis was conducted to determine subregional differences in K_i^{cer} between groups. Details are given in the eAppendix in the [Supplement](#).

Statistical Analysis

Statistical analyses were performed using software programs (Microsoft Excel for Mac, version 15; Microsoft Corp⁵⁰ and SPSS, version 23; SPSS Inc⁵¹). Normality of distribution was confirmed using the Shapiro-Wilk test. Independent-sample *t* tests for normally distributed data and Mann-Whitney tests for nonparametric data were used to examine if there were differences in demographic and clinical variables between groups.

To test for differences in striatal K_i^{cer} between the 3 diagnostic groups, we used analysis of variance, with Tukey test for post hoc pairwise comparisons. To test the association between K_i^{cer} and positive psychotic symptom scores in individuals experiencing a current psychotic episode (irrespective of diagnosis), we used Pearson product moment correlation.

In addition, we restricted this analysis to individuals with bipolar affective disorder and schizophrenia separately. Manic symptoms may be linked to dopamine dysfunction^{25,52,53} and may covary with psychotic symptoms. Therefore, we also conducted partial correlation with the YMRS as a covariate (excluding the “content” item on the YMRS, which indexes psychotic symptoms).

Plots were inspected for outliers, and Cook distance of 4/*n* was used to identify outliers. A 2-tailed significance (α) threshold of 0.05 was used throughout.

Results

Demographic and Clinical Characteristics

In total, 22 individuals were included in the bipolar group, 16 individuals were included in the schizophrenia group, and 22 individuals were included in the healthy control group. All patients received follow-up, which confirmed that diagnoses remained stable.

Demographic details for all participants are listed in [Table 1](#). There were no significant differences between illness groups and healthy volunteers in age, sex, or radioactive isotope dose received.

There were significant differences between the bipolar and schizophrenia groups in the duration of illness and in the PANSS negative symptom and total symptom scores. These data are summarized in [Table 1](#).

Sixteen of 22 individuals in the bipolar group and all 16 individuals in the schizophrenia group fulfilled criteria for a current psychotic episode, with the remainder having a history of a psychotic episode within the last 2 years. Of the 22 individuals with bipolar psychosis, 18 (10 antipsychotic naive and 8 antipsychotic free) were not taking antipsychotics at the time of the PET scan (eAppendix in the [Supplement](#)). Of the 16 individuals with schizophrenia, 14 (11 antipsychotic naive and 3 antipsychotic free) were not taking antipsychotics at the time of the PET scan ([Table 1](#)). Two individuals (one in the bipolar group and one in the schizophrenia group) were taking aripiprazole at the time of the PET scan (one for <2 weeks).

Uptake in the Reference Region and Movement Variables Across Groups

There was no significant association of group with standardized uptake values in the reference region (eAppendix in the [Supplement](#)). In addition, no significant association of group with head motion was observed for the 3 conditions, with mean (SD) values of 13.06 (9.07) mm for the bipolar group, 14.52 (6.46) mm for the schizophrenia group, and 9.61 (9.49) mm for the control group ($F_{2,57} = 1.68$, $P = .20$).

Dopamine Synthesis Capacity Across Groups

There was a significant group difference in K_i^{cer} in the whole striatum ($F_{2,57} = 6.80$, $P = .002$) and its functional subdivisions ([Table 2](#)). Post hoc comparisons showed that the mean (SD) K_i^{cer} in both the bipolar group ($13.18 [1.08] \times 10^{-3} \text{ min}^{-1}$) and the schizophrenia group ($12.94 [0.79] \times 10^{-3} \text{ min}^{-1}$) was

Table 1. Study Participant Demographic and Clinical Details

Variable	Bipolar (n = 22)	Schizophrenia (n = 16)	Controls (n = 22)	P Value
Age, mean (SD), y	23.6 (3.6)	26.3 (4.4)	24.5 (4.5)	.14
Male, No. (%)	13 (59)	14 (88)	14 (64)	NA
Medication status, No. (%)				
Antipsychotic naive or free	18 (82)	14 (88)	NA	NA
Naive	10	11	NA	NA
Free	8	3	NA	NA
Taking antipsychotic	4 (18)	2 (13)	NA	NA
Race/ethnicity, No.				
White	9	5	13	NA
Black	8	7	3	NA
Asian	1	1	4	NA
Mixed	4	3	2	NA
Duration of illness, median (IQR), mo	12 (19)	24 (24)	NA	.04
Prior antipsychotic medication, median (IQR), chlorpromazine dose-years	0.14 (1.33)	0.05 (0.03)	NA	.42
Dose of radioactive isotope injected, mean (SD), MBq	151.37 (13.70)	144.40 (12.29)	154.65 (14.51)	.71
PANSS, mean (SD)				
Positive symptom score	16.05 (8.22)	18.81 (4.12)	NA	.18
Negative symptom score	12.27 (5.40)	17.75 (6.32)	NA	.01
Total symptom score	56.48 (56.68)	72.94 (16.46)	NA	.01
Global Assessment of Functioning, mean (SD)	61.73 (15.94)	46.50 (13.06)	NA	.01

Abbreviations: IQR, interquartile range (from first to third quartile); NA, not applicable; PANSS, Positive and Negative Syndrome Scale.

Table 2. Striatal K_i^{cer} by Study Group for the Bilateral Whole Striatum and Bilateral Functional Striatal Subdivisions

Striatal Region	K_i^{cer} , Mean (SD), $\times 10^{-3} \text{ min}^{-1}$			P value
	Bipolar (n = 22)	Schizophrenia (n = 16)	Controls (n = 22)	
Whole striatum	13.18 (1.08)	12.94 (0.79)	12.16 (0.92)	.002
Associative striatum	13.22 (1.19)	12.95 (0.86)	12.15 (0.89)	.002
Limbic striatum	13.05 (0.90)	12.56 (0.81)	11.95 (1.03)	.001
Sensorimotor striatum	13.16 (1.13)	13.09 (0.91)	12.31 (1.25)	.03

Abbreviation: K_i^{cer} , dopamine synthesis capacity.

significantly elevated relative to controls ($12.16 [0.92] \times 10^{-3} \text{ min}^{-1}$), with large effect sizes (Cohen $d = 1.02$, $P = .002$ in the bipolar group and Cohen $d = 0.91$, $P = .04$ in the schizophrenia group). There was no significant difference in K_i^{cer} in the whole striatum between the bipolar and schizophrenia groups ($P = .73$). The group difference in K_i^{cer} remained significant after excluding individuals taking antipsychotic medication, leaving 18 in the bipolar group and 14 in the schizophrenia group ($F_{2,51} = 6.40$, $P = .003$): the mean (SD) whole striatal K_i^{cer} was $13.17 (1.13) \times 10^{-3} \text{ min}^{-1}$ in the bipolar group, $13.00 (0.73) \times 10^{-3} \text{ min}^{-1}$ in the schizophrenia group, and $12.16 (0.92) \times 10^{-3} \text{ min}^{-1}$ in the control group. Because the schizophrenia group had longer duration of illness than the bipolar group, we ran a secondary analysis of the relationship between whole striatal K_i^{cer} and the duration of illness across the patient groups, which showed no significant relationship ($r = -0.05$, $P = .78$).

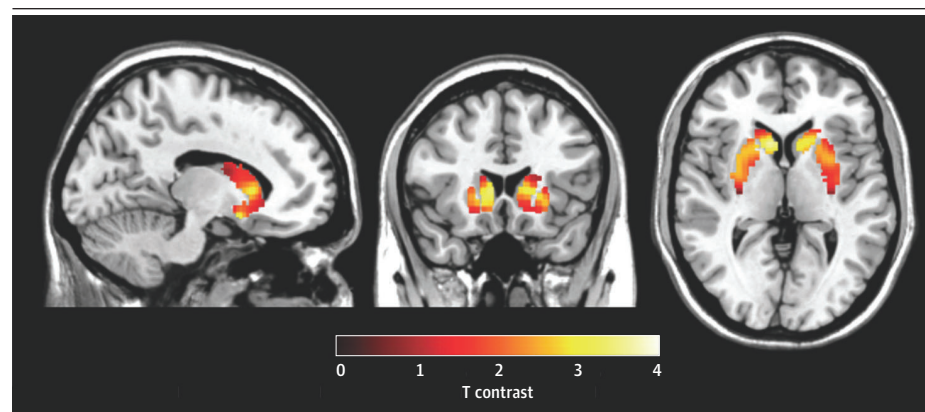
Voxelwise analysis identified significantly greater K_i^{cer} in the bipolar group relative to controls (peak in the right caudate) and in the schizophrenia group relative to controls

(peak in the left putamen) (Figure 1). Relative to controls, the subregional analyses showed significant elevations in all 3 functional striatal subdivisions in the bipolar group but only a suggestion in the associative striatum in the schizophrenia group, with no differences in the substantia nigra for either group (eAppendix in the Supplement).

Relationship Between K_i^{cer} and Psychotic Symptom Severity Across Diagnostic Groups

We found a significant association between whole striatal K_i^{cer} and the PANSS positive subscale symptom severity scores in the combined bipolar and schizophrenia sample of patients experiencing a current psychotic episode (Figure 2), explaining 27% of the variance ($n = 32$, $r = 0.52$, $P = .003$). Cook distance test identified one potential outlier, but removal of this individual did not affect the significance ($r = 0.49$, $P = .01$). There was no relationship between whole striatal K_i^{cer} and the PANSS negative or total symptom scores ($r = 0.13$, $P = .48$ and $r = 0.30$, $P = .10$, respectively).

Figure 1. Voxelwise Comparison of Striatal Dopamine Synthesis Capacity in the Bipolar Psychosis Group Relative to the Control Group



Increased striatal dopamine synthesis capacity was evident in the bipolar psychosis group ($n = 22$) relative to the control group ($n = 22$). The color bar shows the t statistic. The most significant increase was in the right caudate (peak at Montreal Neurologic Institute coordinates $x = 8$, $y = 10$, $z = -8$; t statistic = 3.96, familywise-error corrected $P = .03$). The image was thresholded at $P < .001$ (uncorrected) using a striatal mask (for illustration purposes only). The t statistics for the striatal region are overlaid on a standard structural template in sagittal (left), coronal (middle), and axial (right) views.

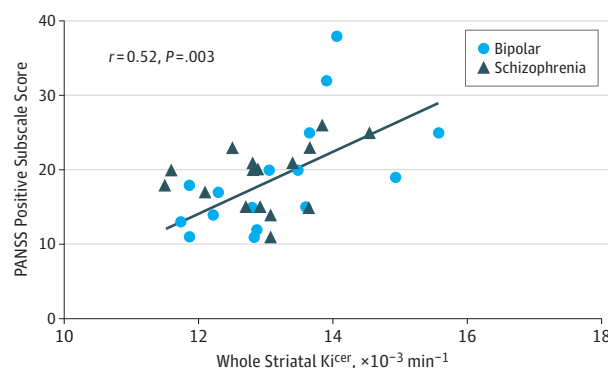
Symptom Correlation in Bipolar Disorder

In the whole sample of individuals with bipolar disorder (with and without a current psychotic episode), there was a nonsignificant relationship between whole striatal K_i^{cer} and the PANSS positive subscale symptom severity score ($n = 22$, $r = 0.42$, $P = .05$). This relationship was significant when the sample was restricted to patients with bipolar disorder with a current psychotic episode, explaining 36% of the variance in positive symptoms ($n = 16$, $r = 0.60$, $P = .01$), and remained significant after covarying for the YMRS (excluding the “content” item) ($r = 0.56$, $P = .046$).

Symptom Correlation in Schizophrenia

Finally, symptom correlation was assessed in the schizophrenia group. In the whole sample of patients with schizophrenia (all experiencing a current psychotic episode), there was no correlation between whole striatal K_i^{cer} and the PANSS positive symptoms ($n = 16$, $r = 0.31$, $P = .24$).

Figure 2. Relationship Between Striatal Dopamine Synthesis Capacity (K_i^{cer}) and Positive Psychotic Symptom Rating in the Bipolar Group Relative to the Schizophrenia Group



There was a significant positive correlation between psychotic (positive) symptom severity and whole striatal K_i^{cer} ($r = 0.52$, $P = .003$). PANSS indicates Positive and Negative Syndrome Scale.

Discussion

Dopamine synthesis capacity was elevated, with a large effect size (Cohen $d = 1.02$), in individuals with bipolar affective disorder and a current or previous psychotic episode compared with healthy controls. In addition, dopamine synthesis capacity was significantly elevated in the schizophrenia group relative to controls. Moreover, dopamine synthesis capacity was associated with the severity of psychotic symptoms in the bipolar group, explaining 36% of the variance in psychotic symptoms. This relationship remained significant after adjusting for the severity of manic symptoms.

The finding herein of no difference in K_i^{cer} in the substantia nigra between the schizophrenia group and controls differs from the results by Howes et al.⁴⁴ However, it should be noted that our study was underpowered to detect this influence.

Our finding of a relationship between positive psychotic symptoms and dopamine synthesis capacity in the combined bipolar and schizophrenia sample but not in the schizophrenia group could be due to a lack of power or inclusion of more

patients with longer illness durations in the schizophrenia group. However, while some studies^{43,44,54} in schizophrenia have found relationships with symptoms, other studies⁵⁵⁻⁵⁸ have not, suggesting that further work is needed to disentangle these correlations.

Strengths and Limitations

A strength of our study is the large number of participants who were antipsychotic naive or free. Furthermore, most individuals were symptomatic and were experiencing an acute psychotic episode at the time of the PET scan. The bipolar and schizophrenia groups were matched for age and medication status, but by chance the schizophrenia group had significantly longer duration of illness. However, there was no relationship between the duration of illness and K_i^{cer} in either group. A concern in first-episode samples is that diagnoses may change. However, in bipolar disorder, more than 90% of diagnoses made on initial presentation are stable 2 years later,⁵⁹ although diagnoses may be more dynamic in the early-intervention services that we recruited from because they aim

to see patients as soon as possible. On follow-up (minimum of 18 months), none of the individuals classified as having either bipolar disorder or schizophrenia had their diagnoses changed, and the validity of diagnosis is strengthened by the difference in negative but not positive symptoms between groups. We did not detect a difference in head motion between groups, although it was greater in absolute terms in the patient groups. Given that motion, especially in the basal ganglia, causes loss of resolution,⁶⁰ any residual motion after motion correction would reduce K_i^{cer} . However, because this would lead to an underestimate of K_i^{cer} , it would not account for our findings.

A potential limitation is the lack of a nonpsychotic control group given possible nonspecific influences of illness, although a prior [¹⁸F]-DOPA study³⁴ in individuals with nonpsychotic mania failed to find a difference compared with controls. Our study was not constructed or powered to detect a difference between bipolar psychosis and schizophrenia.

A small number of individuals were taking antipsychotic medication. The results of preclinical studies^{61,62} suggest that antipsychotic blockade of autoreceptors should cause increased DOPA uptake. However, these studies generally used short exposures to antipsychotics, which may not be equivalent to months of patient exposure. Indeed, there is evidence from animal investigations that 3 weeks of antipsychotic treatment leads to depolarization, decreasing spontaneous firing of dopamine neurons,⁶³ which would reduce dopamine synthesis. Consistent with this finding, the one relevant human study⁶⁴ found that subchronic antipsychotic treatment reduced [¹⁸F]-DOPA uptake in individuals with schizophrenia, which would not explain our results because the effect of antipsychotics would mask any difference compared with controls. However, individuals in that study took only haloperidol for their psychiatric symptoms, and it remains to be determined in patients what effect other antipsychotics have on K_i^{cer} . Nonetheless, K_i^{cer} remained significantly elevated in the patient groups herein when our analysis was restricted to patients who were antipsychotic naive or free, indicating that our findings are not explained by direct treatment influences.

Our outcome measure, K_i^{cer} , indexes the uptake of [¹⁸F]-DOPA into dopamine neurons, as well as its conversion by aromatic acid decarboxylase into [¹⁸F]-dopamine and storage in terminals.⁴⁹ Therefore, the increased K_i^{cer} we report likely reflects an increase in one or more of these processes, as well as a net increase in dopamine synthesis capacity.⁶⁵ However, because tyrosine hydroxylase, not aromatic acid decarboxylase, is the rate-limiting step in dopamine synthesis, this interpretation could be affected if there are alterations in tyrosine hydroxylase levels or activity. Indeed, reduced tyrosine hydroxylase levels could conceivably lead to reduced net dopamine synthesis, despite a compensatory increase in aromatic acid decarboxylase activity detectable with [¹⁸F]-DOPA imaging.

We did not measure plasma input function. There could conceivably be alterations in the delivery of [¹⁸F]-DOPA, although the reference region approach is robust to global differences.⁴⁹ To exclude this potential confounding factor, we

examined the reference region to see whether there was any change across groups and found no difference.

K_i^{cer} reflects a composite of kinetic parameters, including not only blood-tissue transportation (ie, K_1 and k_2) but also relative activity of aromatic acid (DOPA) decarboxylase with respect to [¹⁸F]-DOPA (k_3) and the elimination of decarboxylated [¹⁸F]-DOPA metabolites from the brain (k_{loss}).^{49,66} Therefore, while our findings indicate elevation in these aspects of dopaminergic activity, differences measured for K_i^{cer} could reflect change in one or more of these parameters. However, K_i^{cer} has been shown to correlate well with the [¹⁸F]-DOPA decarboxylation rate (k_3D) derived from the 2-tissue compartmental model, with a metabolite-corrected arterial plasma input function in both normal and pathological conditions.^{67,68} Moreover, if any bias was introduced in K_i^{cer} estimates by the quantification approach, it is likely to be consistent across all 3 groups in our cross-sectional case-control study. However, future studies could address this by measuring the arterial input function.

Conclusions

Our results contrast with prior molecular imaging studies^{34,69} in bipolar disorder finding that dopamine synthesis and release capacity was unaltered. However, in contrast to our study, neither of these prior studies included individuals with bipolar illness with current psychosis, although one study³⁴ included patients with mania and did not find a relationship between manic symptoms and dopamine synthesis capacity. Moreover, the association between K_i^{cer} and psychotic symptoms in our sample remained after controlling for manic symptoms, suggesting that it was not driven by mania. Taken together with the previous results, our findings suggest that elevated dopamine synthesis capacity is linked to psychosis in bipolar disorder. However, a direct comparison between individuals having bipolar disorder with vs without psychosis is needed to definitively test the specificity of our findings to psychosis in bipolar disorder. While we found an association between dopamine synthesis capacity and bipolar psychosis, this result does not imply causality. Further studies are required to determine the relationship between dopamine synthesis capacity and development of psychosis in bipolar disorder.

We found that dopamine synthesis capacity is elevated in psychotic bipolar affective disorder to a degree similar to that in schizophrenia and is related to the severity of psychotic (positive) symptoms. These results extend previous findings that dopamine synthesis capacity is elevated in schizophrenia¹¹ and psychosis associated with temporal lobe epilepsy¹⁰ and increases with the onset of psychosis,¹⁵ suggesting that presynaptic dopamine dysfunction is associated with psychosis across diagnostic categories. This finding provides a potential neurobiological explanation for why antipsychotic drugs, which are all dopamine D_2/D_3 receptor blockers, are effective in bipolar psychosis and schizophrenia⁷⁰⁻⁷² and identifies the regulation of dopamine synthesis as a potential novel drug target for bipolar disorder and schizophrenia.

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Author Contributions: Drs Jauhar and Howes had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Jauhar, Nour, Young, Howes.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Jauhar, Nour, Veronese, Turkheimer, Howes.

Critical revision of the manuscript for important intellectual content: All authors.

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